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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,937	02/15/2002	Herbert M. Dean	dean0202con	3941

23580 7590 01/29/2003  
MESMER & DELEAULT, PLLC  
41 BROOK STREET  
MANCHESTER, NH 03104

EXAMINER

HUI, SAN MING R

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	10/076,937	DEAN ET AL.
	Examiner San-ming Hui	Art Unit 1617
<i>-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --</i>		
<b>Period for Reply</b>		
<b>A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.</b>		
<ul style="list-style-type: none"> <li>- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.</li> <li>- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.</li> <li>- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.</li> <li>- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).</li> <li>- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).</li> </ul>		
<b>Status</b>		
1) <input checked="" type="checkbox"/> Responsive to communication(s) filed on <u>12 November 2002</u> .		
2a) <input checked="" type="checkbox"/> This action is <b>FINAL</b> .                            2b) <input type="checkbox"/> This action is non-final.		
3) <input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11, 453 O.G. 213.		
<b>Disposition of Claims</b>		
4) <input checked="" type="checkbox"/> Claim(s) <u>1-18</u> is/are pending in the application.		
4a) Of the above claim(s) <u>11-16</u> is/are withdrawn from consideration.		
5) <input checked="" type="checkbox"/> Claim(s) <u>18</u> is/are allowed.		
6) <input checked="" type="checkbox"/> Claim(s) <u>1-10 and 17</u> is/are rejected.		
7) <input type="checkbox"/> Claim(s) _____ is/are objected to.		
8) <input type="checkbox"/> Claim(s) _____ are subject to restriction and/or election requirement.		
<b>Application Papers</b>		
9) <input type="checkbox"/> The specification is objected to by the Examiner.		
10) <input type="checkbox"/> The drawing(s) filed on _____ is/are: a) <input type="checkbox"/> accepted or b) <input type="checkbox"/> objected to by the Examiner.		
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).		
11) <input type="checkbox"/> The proposed drawing correction filed on _____ is: a) <input type="checkbox"/> approved b) <input type="checkbox"/> disapproved by the Examiner.		
If approved, corrected drawings are required in reply to this Office action.		
12) <input type="checkbox"/> The oath or declaration is objected to by the Examiner.		
<b>Priority under 35 U.S.C. §§ 119 and 120</b>		
13) <input type="checkbox"/> Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).		
a) <input type="checkbox"/> All b) <input type="checkbox"/> Some * c) <input type="checkbox"/> None of:		
1. <input type="checkbox"/> Certified copies of the priority documents have been received.		
2. <input type="checkbox"/> Certified copies of the priority documents have been received in Application No. _____.		
3. <input type="checkbox"/> Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).		
* See the attached detailed Office action for a list of the certified copies not received.		
14) <input type="checkbox"/> Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).		
a) <input type="checkbox"/> The translation of the foreign language provisional application has been received.		
15) <input checked="" type="checkbox"/> Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.		
<b>Attachment(s)</b>		
1) <input type="checkbox"/> Notice of References Cited (PTO-892)		
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)		
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.		
4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s) _____.		
5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)		
6) <input type="checkbox"/> Other: _____.		

## DETAILED ACTION

The addition of claims 17 and 18 in amendments filed November 12, 2002 is acknowledged.

This application contains claims 11-16, drawn to an invention nonelected with traverse in Paper No. 3. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-18 are pending. Claims 11-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 3.

The expression in claim 10 "a cholesterol lowering agent that is a statin, folic acid, ..., and vitamin B<sub>12</sub>" is not clear. Are folic acid, vitamin B6 and vitamin B12 also cholesterol lowering agent? If they are, then a phrase "a cholesterol lowering agent selected from a statin, folic acid, ..., and vitamin B<sub>12</sub>" should be used.

### ***Warning***

Applicant is advised that should claim 1 be found allowable, claim 17 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim.

See MPEP § 706.03(k). Both claims are drawn to composition comprising the same components.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-10 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pearle (American Heart Journal, 1990 Sep; 120(3):739-742), Carruthers et al. (American Journal of Cardiology, 1993;71:575-581), Abby et al. (Journal of the American Board of Family Practice, 1998; 11(5):391-398), Oakley et al. (The Journal of Nutrition, 1996;126(3): 751S – 755S), and Behounek et al. (US Patent 5,691,375) in view of Rork et al. (US Patent 5,882,682), references of record.

Pearle teaches that beta-blockers such as timolol, metoprolol, atenolol, and propranolol reducing the overall mortality and the incidence of recurrent myocardial infarction (See the abstract; also page 740, col. 1, second paragraph).

Carruthers et al. teaches atenolol reducing the risk of coronary heart disease (See the abstract).

Abby et al. teaches folic acid and vitamin B<sub>6</sub> are useful in reducing the risk of coronary heart disease such nonfatal myocardial infarction and fatal coronary heart disease (See particularly page 395, Table 2).

Oakley et al. teaches vitamin B<sub>12</sub> supplement is useful with folic acid administration to avoid the folic acid adverse effect: B<sub>12</sub> deficiency (See page 3, third and fourth paragraph).

Behounek et al. teaches HMG-CoA reductase inhibitor such as pravastatin is useful in reduce the risk of cardiovascular event (See the abstract).

The references do not expressly the incorporation of beta-blockers such as timolol, metoprolol, atenolol, and propranolol, HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub> into a single once-a-day dosage unit.

Rork et al. teaches a sustained release system that can include beta-blockers such as timolol, metoprolol, atenolol, and propranolol and statin cholesterol lowering agents such as simvastatin, pravastatin, and lovastatin (See col. 6, line 64-66 and col. 7, line 16).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate beta-blockers such as timolol, metoprolol, atenolol,

and propranolol, HMG-CoA reductase inhibitors such as pravastatin, folic acid, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub> into a single once-a-day dosage unit.

One of ordinary skill in the art would have been motivated to incorporate beta-blockers, such as timolol, metoprolol, atenolol, and propranolol, HMG-CoA reductase inhibitors, such as pravastatin, folic acid, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub> into a single once-a-day dosage unit. All the agents herein: different beta-blockers such as timolol, metoprolol, atenolol, and propranolol, HMG-CoA reductase inhibitors such as pravastatin, folic acid, and vitamin B<sub>6</sub> are all known to reduce risk of cardiovascular diseases. Possessing the teachings of the cited prior art, combining two or more agents which are known to be useful to reduce risk of cardiovascular disease individually into a single sustained release, once-daily composition useful for the very same purpose is *prima facie* obvious (See *In re Kerkhoven* 205 USPQ 1069), absent evidence to the contrary. Furthermore, possessing the teaching of Oakley et al., one of ordinary skill in the art would incorporate vitamin B<sub>12</sub> into any folic acid containing composition including the instant composition since vitamin B<sub>12</sub> administration would prevent folic acid adverse effect such as vitamin B<sub>12</sub> deficiency.

### ***Response to Arguments***

Applicant's arguments filed July 30, 2002 averring Rork et al.'s failure to teach a formulation with more than a single active have been fully considered but they are not persuasive. The main reason for motivation for one of ordinary skill in the art to incorporate all the herein claimed compounds into one composition is that all these

ingredients are known to be useful in reducing the risk of cardiovascular disease individually. Therefore, incorporating them into a single composition for the very same purpose would be obvious, absent evidence to the contrary (See *In re Kerkhoven* 205 USPQ 1069). Please note that Rork et al. is not the primary reference. Rork et al. is cited merely to show that once-daily formulation is known in the art. There is no teaching or disclosure in Rork et al. expressly teaches against using more than one active in such once-daily formulation.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the cited prior art, as a whole, renders the instant claims obvious. There is no teaching disclosed in the instant specification for all the claimed agents herein can reduce risk of cardiovascular disease individually.

#### ***Allowable Subject Matter***

Claim 18 is allowed. The cited prior art does not teach or fairly suggest a cholesterol lowering and beta-adrenergic blocking medicament consisting of only two components: a beta-adrenergic blocker and a cholesterol lowering agent that is statin.

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Even though beta-blockers and a statin cholesterol lowering agent are known to reduce cardiovascular disease, one of ordinary skill in the art would not be motivated to not include any excipients or pharmaceutically acceptable carriers into a pharmaceutical composition. Since the herein claimed composition consists only two actives and contains no excipients or pharmaceutically acceptable carriers, the claim is not taught or fairly suggested by the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui  
January 27, 2003

  
SREENI PADMANABHAN  
PRIMARY EXAMINER

1/27/03